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(54) Title: COMPOSITIONS CONTAINING BISMUTH, FOR THE TREATMENT AND PREVENTION OF GASTROINTESTINAL DISORDERS

(57) Abstract

The subject invention encompasses methods for the prevention and treatment of a human or lower animal subject having a gastrointesinal disorder caused or mediated by one or more parasitic protozoa comprising administering bismuth to the subject.

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COMPOSITIONS CONTAINING BISMUTH, FOR THE TREATMENT AND PREVENTION OF GASTROINTESTINAL DISORDERS

BACKGROUND OF THE INVENTION

While bacteria and viruses have long been recognized as a leading cause of diarrhea throughout the world, it was not until about twenty years ago that parasites were considered in the etiology. The importance of diarrhea associated with parasitic protozoa was not realized in the United States, as it was generally believed that this was an illness of impoverished, developing countries. Since that time, parasites such as *Cryptosporidium*, *Giardia*, and *Entamoeba* among others, have been implicated with diarrhea and other gastrointestinal disorders at high incidence rates outside the United States and at an increasing frequency within the United States. For example, in a recent survey of drinking water supplies in fourteen states of the U. S., investigators found one in four to be tainted with *Cryptosporidium parvum*. Health, July/August 1993, p. 14. Therefore, diarrhea and other gastrointestinal disorders associated with parasitic protozoa represent a serious health concern and the need for effective anti-parasitic treatment therapies continues to grow.

It has been discovered by the present invention that the administration of bismuth salts may be effective for the prevention and/or treatment of gastrointestinal disorders caused or mediated by parasitic protozoa. Thus, an object of the present invention is to provide a safe and effective method of preventing and/or treating gastrointestinal disorders caused or mediated by parasitic protozoa. A further object of the invention is to provide such a method comprising the administration of bismuth.

These and other objects of the present invention will become readily apparent from the detailed description which follows.

SUMMARY OF THE INVENTION

The present invention relates to a method for treatment of a human or lower animal subject having a gastrointestinal disorder caused or mediated by one or more parasitic protozoa comprising administering to the subject from about 50 milligrams to about 5000 milligrams of bismuth, per day, for from about 1 to 56 days.

The present invention also relates to a method for prevention in a human or lower animal of a gastrointestinal disorder caused or mediated by

one or more parasitic protozoa comprising administering to the subject from about 50 milligrams to about 5000 milligrams of bismuth, per day, for from about 1 to 28 days.

DETAILED DESCRIPTION OF THE INVENTION

The methods of the present invention comprise the prevention and/or treatment of gastrointestinal disorder caused or mediated by one or more parasitic protozoa. Such gastrointestinal disorders are prevented and/or treated by the administration of bismuth. The components of the present invention are more fully defined below.

Gastrointestinal Disorder

The term "gastrointestinal disorder", as used herein, encompasses any infection, disease or other disorder of body, typically of the upper and/or lower gastrointestinal tract, caused or mediated by one or more parasitic protozoa. Such disorders include one or more of the following conditions: diarrhea, abdominal pain and/or cramping, flatulence, nausea, abdominal distention, fever, constipation, blood, mucus and/or pus present in feces, vomiting, gastroenteritis, weight loss, anorexia, malaise, and any other condition commonly associated with infection by parasitic protozoa.

In immunocompromised subjects and children, gastrointestinal disorders caused or mediated by parasitic protozoa may be more severe and life threatening than the common disorders listed above. Therefore, the term "gastrointestinal disorder" also includes any condition commonly associated with protozoa infection in immunocompromised subjects and children, including but not limited to, acute diarrhea, dehydration, electrolyte imbalance, colitis, and fatal necrosis of the intestine.

Parasitic Protozoa

Protozoa are unicellular, eucaryotic organisms which contain a nucleus, or nuclei, and cytoplasm. Four groups of Protozoa contain parasites which are contemplated in the present invention. These organisms are fully described in Zinsser Microbiology, 20th Edition, 1163-1173, (1992) and T. L. Kuhls, M.D., "Protozoal Infections of the Intestinal Tract in Children", Advances In Pediatric Infectious Diseases, vol. 8, 177-202, (1993), both of which are incorporated herein by reference. The term "parasitic protozoa", as used herein, refers to Protozoa of the phlya Sarcomastigophora such as *Entamoeba*, *Giardia*, *Dientamoeba*, and *Blastocystis*; Ciliophora such as *Balantidium*; Apicomplexa such as *Isospora*

and *Cryptosporidium*; and Microspora such as *Enterocytozoon*. Preferred parasitic protozoa are *Entamoeba*, *Cryptosporidium*, *Giardia*, *Isospora*, and combinations thereof. Most preferred parasitic protozoa are *Entamoeba*, *Cryptosporidium*, *Giardia*, and combinations thereof.

Diagnosis of gastrointestinal disorders caused or mediated by parasitic protozoa may be accomplished by any method commonly used in the medical community. Such methods are fully described in Zinsser Microbiology, and T.L. Kuhls, M.D. "Protozoal Infections of the Intestinal Tract in Children", as referenced above.

Bismuth

The methods of treatment and/or prevention in the present invention involve administration of bismuth. As used herein, the quantity of bismuth is by weight of elemental bismuth.

The preferred duration of bismuth administration will vary according to the specific gastrointestinal disorder to be treated and the physical condition of the subject being treated. In general, as a method of treatment, bismuth may be administered in an amount of from about 50 milligrams to about 5000 milligrams, and preferably from about 50 milligrams to about 2500 milligrams, per day, for from about 1 to about 56 days, preferably for from about 2 to about 28 days, and most preferably for from about 7 to about 21 days.

In general, as a method of prevention, bismuth may be administered in an amount of from about 50 milligrams to about 5000 milligrams, and preferably from about 50 milligrams to about 2500 milligrams, per day, for from about 1 to about 21 days, and preferably for from about 1 to about 14 days. In a method of prevention, bismuth may be administered prior to potential exposure to parasitic protozoa. Such administration of bismuth may vary depending on the likelihood of parasitic protozoa exposure and condition of the subject and may be commenced at any time deemed beneficial by the medical community including from about 1 to about 7 days, from about 2 to about 5 days, and from about 3 to about 4 days, prior to potential exposure.

In the present methods, bismuth may be in the form of a pharmaceutically-acceptable salt or may be in the form of an organic complex which contains bismuth as an active ingredient. Such organic complexes include 2,2'-spirobi[1,3,2-benzodoxabismole]. Preferably, bismuth is administered in the present methods as a pharmaceutically-

acceptable salt. Such bismuth salts include bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgalate, bismuth subnitrate, bismuth tartrate, bismuth subsalicylate, and mixtures thereof. Bismuth citrate, bismuth subcitrate, tripotassium dicitrato bismuthate, bismuth tartrate, bismuth subsalicylate, and mixtures thereof are preferred bismuth salts for use in this invention.

The bismuth useful herein may be administered alone, or in combination with other pharmaceutically-acceptable components in a bismuth-containing composition. A variety of such compositions containing bismuth salts are commercially available.

Such compositions include DeNol, containing tripotassium dicitrato bismuthate (by Brocades); Bislumina, containing bismuth aluminate (by Mazuelos); Roter, containing bismuth subnitrate (by Roterpharma); Devrom®, containing bismuth subgallate (by The Parthenon Co., Inc.); and Pepto-Bismol®, containing bismuth subsalicylate (by The Procter & Gamble Company).

As used herein, the term "administering" refers to any method which, in sound medical practice delivers the compounds or compositions used in this invention to the subject to be treated in such a manner so as to be effective in the treatment of the gastrointestinal disorder. Preferably, the bismuth is administered orally.

The following non-limiting examples illustrate the methods and uses of the present invention.

EXAMPLE I

A human subject, suffering from severe diarrhea, is treated by a method of the present invention. Fecal samples are taken from the subject and analyzed for the presence of intestinal parasites, including organism eggs, cysts, sporozoites, etc. Clinical parasitology specimens reveal the presence of *Cryptosporidium parvum*. The subject is then treated by administering a composition containing bismuth subsalicylate, sold by The Procter & Gamble Company under the name "Pepto-Bismol®". The composition, in liquid form, is administered four times daily in equal doses delivering approximately 2500 milligrams of bismuth per day, for 21 days. Thereafter, fecal samples from the subject are analyzed again, finding no trace of parasitic infection. The subject remains asymptomatic, and another fecal analysis performed 5 months later is normal.

In the above example, tripotassium dicitrato bismuthate, bismuth tartrate, bismuth citrate, and bismuth subnitrate are substituted, respectively, for bismuth subsalicylate, with substantially similar results.

EXAMPLE II

A three-year-old child with diabetes and in a day care center is suffering from chronic diarrhea, and abdominal distention. Analysis of fecal specimens shows the presence of *Giardia lamblia*. The infection is diagnosed and treated by orally administering approximately 400 milligrams of bismuth in the form of bismuth subcitrate ("DeNol", sold by Brocades), in four equal doses daily, for about 28 days. Thereafter, fecal samples from the subject are analyzed again, finding no trace of parasitic infection.

EXAMPLE III

A Peace Corps volunteer preparing to travel to a developing country with sub-standard sanitation and water purification systems has a fecal sample clinically analyzed for the presence of *Giardia lamblia*, *Cryptosporidium parvum*, and *Entamoeba histolytica*. Clinical results show no evidence of the parasites. The subject is given approximately 1200 milligrams of bismuth, (administered as bismuth subsalicylate in the composition Pepto-Bismol®, sold by The Procter & Gamble Company), in four equal doses daily, for about 21 days. Upon return to the U.S., approximately 30 days after the initial clinical analysis, the subject remains asymptomatic. Fecal samples from the subject are analyzed and no evidence of parasitic infection is found.

1. The use of from 50 milligrams to 5000 milligrams of bismuth per day for from 1 to 56 days for the manufacture of a composition for the treatment of a human or lower animal subject having a gastrointestinal disorder caused or mediated by one or more parasitic protozoa.

2. The use according to Claim 1 wherein the bismuth is to be administered at a level of from 0 milligrams to 2500 milligrams, per day.

3. The use according to Claim 1 or 2 wherein the bismuth is selected from the group consisting of bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgalate, bismuth subsalicylate, bismuth tartrate, and mixtures thereof.

4. The use according to Claims 1-3 wherein the parasitic protozoa are selected from the group consisting of *Cryptosporidium, Giardia, Entamoeba, Isospora*, and combinations thereof.

5. The use according to Claims 1-4 wherein said bismuth prevents gastrointestinal disorder caused or mediated by one or more parasitic protozoa comprising administering to the subject from 50 milligrams to 5000 milligrams of bismuth, per day, for from 1 to 21 days.

6. The use according to Claims 1-5 wherein the bismuth is administered at a level of from 50 milligrams to 2500 milligrams, per day.

7. A method for treatment of a human or lower animal subject having a gastrointestinal disorder caused or mediated by one or more parasitic protozoa comprising administering to the subject from about 50 milligrams to about 5000 milligrams of bismuth, per day, for from about 1 to 56 days.

8. The method of Claim 7 wherein the bismuth is administered at a level of from about 50 milligrams to about 2500 milligrams, per day.

9. The method of Claim 7 wherein the bismuth is selected from the group consisting of bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgalate, bismuth subsalicylate, bismuth tartrate, and mixtures thereof.

10. The method of Claim 7 wherein the parasitic protozoa are selected from the group consisting of *Cryptosporidium, Giardia, Entamoeba, Isospora*, and combinations thereof.

11. A method for prevention in a human or lower animal subject of a gastrointestinal disorder caused or mediated by one or more parasitic protozoa comprising administering to the subject from about 50 milligrams to about 5000 milligrams of bismuth, per day, for from about 1 to 21 days.

12. The method of Claim 11 wherein the bismuth is administered at a level of from about 50 milligrams to about 2500 milligrams, per day.

13. The method of Claim 11 wherein the bismuth is selected from the group consisting of bismuth aluminate, bismuth subcarbonate, bismuth subcitrate, bismuth citrate, tripotassium dicitrato bismuthate, bismuth subgalate, bismuth subsalicylate, bismuth tartrate, and mixtures thereof.

14. The method of Claim 11 wherein the parasitic protozoa are selected from the group consisting of *Cryptosporidium, Giardia, Entamoeba, Isospora*, and combinations thereof.

INTERNATIONAL SEARCH REPORT

Internatior pplication No
PCT/US 96/06488

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K33/24 A61K31/29 A61K31/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	N. ENGL. J. MED., 1983, 308/16 (967), USA, XP000602894 PITLIK S.D. ET AL: "Cryptosporidial cholecystitis" see the whole document ---	1-14
X	INFECT. DIS. CLIN. NORTH AM., 1993, 7/3 (569-586), USA, XP000603005 WITTNER M. ET AL: "Parasitic infections in AIDS patients: Cryptosporidiosis, isosporiasis, microsporidiosis, cyclosporiasis" see page 572, paragraph 6 - page 573, paragraph 1 --- -/--	1-14

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 1996	09. 10. 96

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Internation pplication No
PCT/US 96/06488

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	REV. INFECT. DIS., 1990, 12/SUPPL. 1 (S80-S86), USA, XP000602908 STEFFEN R.: "Worldwide efficacy of bismuth subsalicylate in the treatment of travelers' diarrhea" see page S85, column 2, paragraph 4 - page S86, column 1 ---	1-14
A	US,A,4 940 695 (COVENEY LEILA D ET AL) 10 July 1990 see abstract ---	1-4
A	EP,A,0 103 836 (HERSCHLER R J) 28 March 1984 see page 15 - page 16, paragraph 1 ---	1-14
A	BE,A,654 814 (R. SCHAPIRO) 15 February 1965 see claim 1 see page 3, paragraph 9 - page 4, paragraph 1 -----	1-14

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/06488

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 7-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US 96/06488

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-4940695	10-07-90	NONE		
EP-A-0103836	28-03-84	US-A-	4514421	30-04-85
		AU-B-	564536	13-08-87
		AU-A-	2039683	04-04-84
		AU-B-	599670	26-07-90
		AU-A-	7473287	08-10-87
		CA-A-	1219218	17-03-87
		SU-A-	1443788	07-12-88
		WO-A-	8401105	29-03-84
		US-A-	4973605	27-11-90
		US-A-	4559329	17-12-85
		US-A-	4616039	07-10-86
BE-A-654814	15-02-65	FR-M-	118	
		FR-M-	119	